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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/657,006	DINGIVAN ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *83-114* is/are pending in the application.

4a) Of the above claim(s) *98,99 and 108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83-97,100-107 and 109-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7-22-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

   Applicant's amendment to the specification, claims and argument filed on July 22, 2008 has been entered.

   Claims 1-82 have been canceled.

   Claims 83-114 have been added.

2. The prior election of species requirements as to the species of "T cell malignancy to be treated", "cancer therapeutic" and "therapeutic agent or drug conjugated to the anti-CD2" are withdrawn upon further consideration and in view of applicant's amendment to the claims.

   Moreover, upon further consideration, the species of therapy to be administered with the anti-CD2 antibody which is "hematopoietic stem cell transplantation" has been rejoined to the previously elected therapy to be administered with the anti-CD2 antibody "aggressive combination chemotherapy".

   Thus, claims 83-97, 100-107 and 109-114 are under examination as they read on a method of treating adult T cell leukemia comprising administering to a human in need thereof an effective amount of an anti-CD2 antibody, wherein the elected species of anti-CD2 antibodies are "MEDI-507" and "an anti-CD2 antibody with the proviso that said antibody is NOT MEDI-507 but it has the same properties as MEDI-507"; the elected species of adult T cell leukemia patient to be treated is one with "a T cell malignancy refractory or non-responsive to chemotherapy" and the elected species of therapy to be administered with the anti-CD2 antibody are "aggressive combination chemotherapy" or "hematopoietic stem cell transplantation".

   Moreover, claims 98, 99 and 108 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species of invention, there being no allowable generic or linking claim. Applicant's elections were made **without** traverse in the replies filed on July 21, 2006 and November 13, 2007.

3. This Office Action is in response to applicant's amendment to the specification, claims and arguments filed July 22, 2008.

   The previous rejections of record can be found in the Office Action mailed February 22, 2008.

4. The previous rejection under 35 U.S.C. § 112, 1st paragraph, enablement, is withdrawn in view of applicant's argument and amendment to the claims and for the reasons put forth below.

In particular, with respect to enabling the skilled artisan to make the full *length chain* of siplizumab, applicant asserts at page 7, 3rd paragraph of their remarks filed July 22, 2008 that "the present application teaches that MEDI-507 is disclosed in International publication No. WO 99/03502 ("Bazin")...and incorporates these references into the specification. See page 64, lines 29-31 of the specification of the present application."

Applicant goes on to further assert at page 8, 4th paragraph of their remarks that "Bazin discloses the vectors that express the humanized heavy chain constant region and light chain constant region of MEDI-507 and methods for producing MEDI-507 ...Applicants submit that the sequences for those constant regions were known to one of skill in the art as of the effective filing date of the present application. Applicants direct the Examiner's attention to the following references for a description of the nucleotide and/or amino acid sequences of the humanized light chain and heavy chain constant regions of MEDI-507:(1) Hieter *et al.,*...In particular, Applicants direct the Examiner's attention to ...Figure 5 of Hieter, for the nucleotide sequences of the humanized...light chain constant regions of MEDI-507..."

However applicant's argument, per se, is not found convincing.

In particular, while Bazin WO 99/03502 discloses at page 81, last paragraph that the light chain of MEDI-507 was created by inserting the appropriate humanized Vl domain into the light chain expression vector licensed from the MRC "hcmv-VlLys-kr-neo" which "contains a genomic clone of the human kappa constant region and the humanized Vl domain of antilysozyme as a HindIII-BamHI fragment...Maeda, et al., 1991, Hum. Antibod. Hybridomas, Vol. 2, pgs. 124-134)," neither Bazin nor Maeda (submitted in an IDS with applicant's response of July 22, 2008) teach the particular human kappa constant region allele contained within the "hcmv-VlLys-kr-neo" vector. This is of particular importance because there are three alleles (Inv1, Inv2 and Inv3) of human kappa constant region as disclosed by Hieter el al. (Cell. 1980 Nov;22(1 Pt 1):197-207, submitted in an IDS with applicant's response of July 22, 2008).

Thus, in the absence of knowledge as to which particular allele of human kappa was used to make the "hcmv-VlLys-kr-neo" vector, the skilled artisan would not be able to make the MEDI-507/siplizumab antibody as of applicant's earliest effective filing date.

Nevertheless, in reviewing the knowledge in the art, the examiner has determined that the "hcmv-VlLys-kr-neo" vector was known to contain the Inv3 allele of the human kappa constant region as evidenced, for example, by the teachings of Chestnut et al., (WO 94/25067, cited herewith), see in particular, page 63, 1st paragraph to the paragraph bridging pages 63-64 as well as the paragraph bridging pages 64-65.

Thus, while applicant's argument concerning the ability of the skilled artisan to make the light chain of siplizumab/MEDI-507, per se, was not found convincing, in view of the knowledge in the art as whole as of the effective filing date of the instant application, the previous rejection under 112, 1st paragraph is withdrawn.

5. The previous rejection under 35 U.S.C. § 112, 2nd paragraph is withdrawn in view of applicant's argument and amendment to the claims. In particular, applicant's argument that the term "siplizumab," would be considered definite by one of ordinary skill in the art is found convincing because "siplizumab" was and is the art recognized generic name for MEDI-507 based on the World Health Organization's International Nonproprietary naming scheme.

6. The previous rejections under 35 U.S.C. § 103(a) over "Dang in view of..." are withdrawn in view of applicant's cancellation of all previously pending claims and introduction of new claims. That said, a new grounds of rejection under 35 U.S.C. § 103(a) over "Dang in view of..." has been applied to the new claims, essentially for the same reasons put forth in the Office Action mailed February 22, 2008 as put forth further below.

   The previous rejection under 35 U.S.C. § 103(a) over "PR Newswire in view of..." is withdrawn in view of applicant's cancellation of all previously pending claims and introduction of new claims.

   New Grounds of Rejection are put forth below.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

   > (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 83-93, 96, 97, 100-107 and 109-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dang (US 2003/0031665) in view of Shirono et al. (Blood. 1989 May 1;73(6):1664-71), Alberola-Ila et al. (J Immunol. 1991 Feb 15;146(4):1085-92), Branco et al. (Transplantation. 1999 Nov 27;68(10):1588-96), Bazin et al. (WO 99/03502) the instant specification at page 3, 1st paragraph, and further in view of Hohlfeld et al., (Proc Natl Acad Sci U S A. 2004 Oct 5;101 Suppl 2:14599-606), Qu et al., (Methods. 2005 May;36(1):84-95), essentially for the reasons of record as put forth in the previous Office Action mailed February 22, 2008.

   Applicant argues that one of ordinary skill in the art would not have been motivated to practice the claimed invention and would not have had a reasonable expectation of success in

doing so in view of the reference teachings and the knowledge in the art (see applicant's remarks filed July 22, 2008, page 11, last paragraph to page 12).

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed February 22, 2008.

More specifically, applicant argues Shirono teaches antigens other than CD2 are also overexpressed on adult T cell leukemia cells, and that one of ordinary skill in the art would not have been motivated to select CD2 as the target antigen from among the various overexpressed molecules taught by Shirono (see the paragraph bridging pages 11-12 of applicant's remarks).

Applicant's argument is not found convincing because:

1. applicant's assertion that the teachings of Shirono provide no motivation to select CD2 as the target antigen is incorrect, and

2. applicant also neglects to consider the motivation that one of ordinary skill in the art would have had to use siplizumab/MEDI-507 to treat adult T cell leukemia given the teachings of the other applied references.

With respect to point 1 above, the examiner submits that one of ordinary skill in the art would have had sufficient motivation to target the CD2 antigen in a method of treating adult T-cell leukemia in view of the teachings of Shirono, per se. More specifically, as shown in Figures 1 and 2 of Shirono, as opposed to the other antigens profiled, the vast majority of adult T-cell leukemia cells are (a) positive for CD2 by immunofluorescence (see Fig. 1) and (b) at the same time appear to overexpress greater absolute numbers of CD2 as measured by mean fluorescence intensity than do normal T cells (see Fig. 2).

This expression profile is distinct from the other markers tested in Shirono and would have provided one of ordinary skill in the art with sufficient motivation to select CD2 as a target antigen for treating adult T cell leukemia.

With respect to point 2 above, applicant neglects to address that additional motivation to treat adult T cell leukemia with an anti-CD2 antibody arises from the known ability of siplizumab/MEDI-507 to deplete, in vivo, human T cells, in particular activated human T cells to which is binds, even in the absence of further conjugation to a cytotoxic moiety (see the teachings of Branco and Bazin as put forth in the previous Office Action mailed February 22, 2008 and in Sections 10 and 12 below).

Thus, one of ordinary skill in the art would have been motivated to practice the claimed invention not only because CD2 was a good target for antibody based immunotherapy of adult T cell leukemia, but also because the anti-CD2 antibody siplizumab was known to be an attractive candidate for antibody based immunotherapy in general.

For example, given that siplizumab had confirmed T cell depleting activity as a "naked" antibody, one of ordinary skill in the art would consider siplizumab an attractive candidate for the treatment of leukemias/lymphomas of T cell origin. This is because conjunction of antibodies to therapeutic moieties adds an additional level of complexity to industrial antibody production which can only serve to further complicate (and thus add to the cost of) what is already a challenging field of endeavor (see, e.g., Qu et al., in particular page 93, right column, 1st paragraph).

Thus, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated to treat ATL with siplizumab, or an antibody that competes with siplizumab for binding to CD2, given the reference teachings.

Applicant further argues overexpression of CD2 on adult T cell leukemia cells does not necessarily provide one of ordinary skill in the art with a reasonable expectation of success in treating adult T cell leukemia with an anti-CD2 antibody, pointing to statements in the previous Office Action mailed February 22, 2008 concerning the use of anti-CD2 antibodies to treat the T cell malignancy ***multiple sclerosis*** which was encompassed by the breadth of the claims subject to examination in the Office Action mailed February 22, 2008 (see applicant's remarks, ibid, and the footnote on page 12 of applicant's remarks).

Applicant's argument is not found convincing because applicant has misconstrued the previous rejection concerning the use of anti-CD2 antibodies to treat the T cell malignancy ***multiple sclerosis***.

Applicant's assertion in the footnote at the bottom of page 12 that "The Examiner acknowledges that treatment with an antibody directed to any antigen is not necessarily effective in deleting a cell population overexpressing that antigen," is not correct.

The examiner made no such assertion in the previous Office Action. Rather, what was said about the use of anti-CD2 to treat multiple sclerosis as stated on page 4, 4th paragraph of the previous Office Action is as follows: "[w]hile CD3 and CD4, like CD2, are known in the art to be widely expressed on both naive and activated T cells, the use of anti-CD3 and anti–CD4 antibodies to treat T cell malignancies such as multiple sclerosis has not been successful (see Wiendl et al., BioDrugs. 2002;16(3):183-200, in particular, page 196). Given the inability of anti-CD3 and anti–CD4 antibodies to treat multiple sclerosis, the skilled artisan would consider treating multiple sclerosis with yet another antibody that binds a widely expressed T cell antigen, anti-CD2 antibody, to be highly unpredictable."

In this regard, it is noted that post-filing date art shows clinically successful multiple sclerosis treatments function by strengthening regulatory T cell mediated suppression of autoimmunity rather than simply deleting all T cells from the immune repertoire, which will at the same time delete beneficial regulatory T cells as well (see, e.g., Hohlfeld, in particular page 14605, right column, 1st paragraph). This illustrates how treating multiple sclerosis by

depleting T cells is qualitatively different from treating adult T cell leukemia by depleting T cells.

Applicant further argues lack of reasonable expectation of success at page 12, 1st paragraph of their remarks because "[t]he example section of the specification of the present application demonstrates that the administration of an antibody immunospecific for IL-2Rα, another antigen overexpressed by T-cells from ATL patients, is not as effective as the administration of an antibody immunospecific for human CD2 for the treatment ATL..." Applicant then goes on to describe how MEDI-507 outperformed a particular anti-IL-2Rα antibody in a murine model of adult T cell leukemia. Based on these assertions applicant concludes, "[t]hus, merely because an antigen is overexpressed on T-cells of ATL patients does not provide one ordinary skill in the art with a reasonable expectation that an antibody against that antigen would be successful to treat adult T-cell leukemia."

Applicant's argument is not found convincing because it is a non-sequitur.

The examiner submits that the data presented in the instant specification serves to validate the reasonable expectation of success that one of ordinary skill in the art would have had with respect to treating adult T-cell leukemia with either anti-CD2 or anti-IL-2Rα. It does not support that anti-IL-2Rα would not have some degree of success in treating adult T-cell leukemia.

Furthermore, new claim 98 which recites a method of treating adult T cell leukemia consisting essentially of administering an anti-CD2 antibody and an anti-IL-2Rα antibody is inconsistent with applicant's argument.

In conclusion, the instant claims are rejected as unpatentable over Dang in view of Shirono, Alberola-Ila, Branco and Bazin.

9. Claims 94 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dang (US 2003/0031665) in view of Shirono et al. (Blood. 1989 May 1;73(6):1664-71), Alberola-Ila et al. (J Immunol. 1991 Feb 15;146(4):1085-92), Branco et al. (Transplantation. 1999 Nov 27;68(10):1588-96), Bazin et al. (WO 99/03502), the instant specification at page 3, 1st paragraph, Hohlfeld et al., (Proc Natl Acad Sci U S A. 2004 Oct 5;101 Suppl 2:14599-606, cited herewith) and Qu et al., (Methods. 2005 May;36(1):84-95) as applied to claims 83-93, 96, 97, 100-107 and 109-114 in Section 8 above, and further in view of Taguchi et al. (J Acquir Immune Defic Syndr Hum Retrovirol. 1996 Jun 1;12(2):182-6), essentially for the reasons of record as put forth in the Office Action mailed February 22, 2008.

Applicant's arguments and the examiner's rebuttal as to the teachings of Dang, Shirono, Alberola-Ila, Branco and Bazin are given above.

With respect to the teachings of Taguchi, applicant argues they do not make up for the alleged deficiencies of Dang, Shirono, Alberola-Ila, Branco and Bazin references.

Applicant's argument is not found convincing for the reasons put forth in Section 8 above and further in the previous Office Action mailed February 22, 2008.

Thus, the instant claims are rejected as unpatentable over Dang in view of Shirono, Alberola-Ila, Branco, Bazin and Taguchi.

10. Claims 83, 84, 87-97, 106, 107, 109-112 and 114 are rejected under 35 U.S.C. § 103(a) as unpatentable over Megan Sykes (WO 02/40049) in view of Borg et al. (Br J Haematol. 1996 Sep;94(4):713-5), Bazin et al. (WO 99/03502), and further in view of Taber's Cyclopedic Medical Dictionary, ed. Thomas L Clayton, 17th edition, F.A. Davis Company, 1993, p 970-71, Shirono et al. (Blood. 1989 May 1;73(6):1664-71), Branco et al., (Transplantation. 1999 Nov 27;68(10):1588-96) and the instant specification at page 3, 1st paragraph, page 68, 1st paragraph and page 69, last paragraph.

As a preliminary matter, it is noted for examination purposes that "BTI-322" and "Lo-CD2a" and "BTI-322/Lo-CD2a" are laboratory designations used in the art for a rat anti-human CD2 antibody. "MEDI-507," known by the generic non-propriety designation "siplizumab" is a humanized version of "BTI-322/Lo-CD2a" with the same epitope specificity and avidity according to the teachings of Branco at page 1590, left column, 1st paragraph.

It is further noted that claims 87, 88 and dependent claims thereof, given their broadest reasonable interpretation consistent with the instant specification, encompass in their breadth a method of treating adult T cell leukemia consisting essentially of administering to a human in need thereof an effective amount of siplizumab/anti-CD2 antibody that is not siplizumab and a therapy, wherein the therapy is, for example, "immunotherapy".

The instant specification does not define the meaning of the term "immunotherapy". The most descriptive portion of the specification discloses at page 69, last paragraph "…immunotherapy (e.g., anti-Tac(Fv)-PE40KDEL; Ohno N. *et al.* ,2002, *Leuk. Lymphoma,* 43(4):885-8)…"

Thus, according to the instant specification, a non-limiting example of immunotherapy is an anti-Tac antibody, i.e., an anti-IL-25Rα antibody.

Moreover, the term "immunotherapy" is used broadly in the art to refer to any treatment that produces or enhances immunity, e.g., treatments that produce or enhance cellular and/or humoral immunity (see, e.g., Taber's Cyclopedic Medical Dictionary, p 970, cited herewith, and the definitions of "immunotherapy" found on the web according to Google.com as of November 9, 2008, www.google.com/search? hl=en&rls=GGLD%2CGGLD%3 A2004-30% 2CG GLD%3Aen&q=define %3A+immunotherapy, attached herewith).

Furthermore, according to the instant specification at page 68, 1st paragraph, the invention provides methods of treating T-cell malignancies comprising administering MEDI-507 and

(emphasis added): "one or more standard or experimental therapies for T-cell malignancies. ***Standard and experimental therapies of T cell malignancies that can be used in the methods and compositions of the invention include, but are not limited to***, antibody therapy *(e.g.,* Campath®, anti-Tac…aggressive combination chemotherapy with or without cytotoxic agents…***hematopoietic stem cell transplantation***…"

Thus, claims 87, 88 and dependent claims thereof, given their broadest reasonable interpretation consistent with the instant specification and the plain meaning of the term "immunotherapy" as its used in the art, encompass in their breadth, for example, a method of treating adult T cell leukemia consisting essentially of administering to a human in need thereof an effective amount of siplizumab, and an immunotherapy, such as "hematopoietic stem cell transplantation".

With this claim construction in mind, the following rejection is put forth:

Sykes teaches a method of treating hematologic disorder, e.g., a leukemia, comprising administering one or more myeloreductive, non-myeloablative agents such as chemotherapeutic agents, followed by administration of hematopoietic stem cells and a T cell depleting agent, such as the anti-CD2 antibody MEDI-507, or an anti-CD2 antibody which overlaps or binds the epitope recognized by BTI-322, to induce a graft-versus-leukemia effect while minimizing graft-versus-host disease (see Sykes, in particular page 9, 1st paragraph; paragraph bridging pages 9-10 and the 2nd paragraph on page 10; page 11, 1st-last paragraphs; page 19, 1st paragraph; the paragraph bridging pages 21-22 and claims 8 and 28).

Sykes further teaches that the anti-T cell antibody can be administered prior to, at the same time, or after administration of donor hematopoietic stem cells, for example, Sykes teaches administration of anti-T cell antibodies about 1, 2, 3, 4 or 5 days prior to and/or after stem cell transplantation (see page 3rd and 4th paragraphs).

Lastly, Sykes teaches allogeneic bone marrow transplantation is a treatment option for patients with hematologic malignancies refractory or non-responsive to chemotherapy (see paragraph bridging pages 2-3).

Sykes does not explicitly teach a method of treating adult T-cell leukemia, including adult T-cell leukemia refractory or non-responsive to chemotherapy, or the particular antibody dosing recited in the claims.

However, it would have been obvious to one of ordinary skill in the art that any hematologic cancer, including a T cell leukemia such as adult T cell leukemia, can be treated according to the teachings of Sykes, as it is well known to one of ordinary skill in the art that a variety of hematologic cancers are amenable to treatment via hematopoietic stem cell or bone marrow transplantation.

For example, Borg teaches the treatment of adult T cell leukemia in a patient

comprising administering a combination of chemotherapeutic agents to affect myeloablation followed by administration of allogeneic bone marrow from an HLA-compatible sister so as to induce a graft-versus-leukemia effect (see Borg, page 714, column bridging paragraph and page 715, left column 2nd and 3rd paragraphs).

While the patient treated in Borg was HLA-compatible, 70-75% of patients lack an HLA-matched donor as taught by Sykes at page 9, 1st paragraph. Thus, for those adult T cell leukemia patients one of ordinary skill in the art would be motivated to make use of the method taught by Sykes which enables use of allogeneic hematopoietic stem cell transplantation from HLA mismatched donors.

Furthermore, one of ordinary skill in the art would have been motivated, and would have had a reasonable expectation of success in using either MEDI-507/siplizumab or an anti-CD2 antibody which overlaps or binds the epitope recognized by BTI-322 in a method of treating adult T-cell leukemia by following the teachings of Sykes in view of Bazin.

In particular, Bazin teaches LO-CD2a/BTI-322 effectively depletes $CD2^+$ lymphocytes in vivo (see page 38, 4th paragraph to page 39, 1st paragraph (human) and page 31, 5th paragraph to the paragraph bridging pages 36 and 37 and Figure 13 (non-human primates), and Lo-CD2a has been administered to patients to successfully treat GVHD (see page 45, 1st paragraph). Bazin also demonstrates the equivalent abilities of LO-CD2a/BTI-322 and MEDI-507 to immunodeplete $CD2^+$ lymphocytes in mice (see, in particular, page 89, 3rd paragraph to page 90).

Moreover, with respect to the particular antibody dosing recited in claims 112, Bazin teaches the *in vivo* immunodepletion of $CD2^+$ lymphocytes and treating GVHD with LO-CD2a/BTI-322, or an antibody that binds the same epitope or any part thereof, in humans using antibody dosages encompassed by the rejected claims (see, Bazin, ibid).

Furthermore, as taught by Shirono at page 1664, left column, 1st paragraph, patients suffering from acute adult T-cell leukemia die within 3 months despite intensive chemotherapy, thus acute adult T-cell leukemia is refractory or non-responsive to chemotherapy. One of ordinary skill in the art would be highly motivated to make use of the method of Sykes to treat such a patient because, as taught by Sykes, allogeneic bone marrow transplantation may be the only remaining treatment option for patients with hematologic malignancies refractory or non-responsive to chemotherapy.

Lastly, it is noted that the phrase "aggressive combination chemotherapy" as recited in claims 94 and 95, given its broadest reasonable interpretation consistent with the instant specification, see, e.g., page 68, 1st paragraph, will be interpreted as encompassing chemotherapy with two or more chemotherapeutic agents, which is taught by Sykes.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention.

Applicant's arguments put forth their Remarks filed July 22, 2008, insofar as they are germane to the rejection given above, are addressed below.

Insofar as applicant continues to argue that the applied references fail to teach or suggest the claimed invention because they allegedly teach the prevention of graft versus host disease following bone marrow transplantation without sufficiently teaching or suggesting the treatment of adult T cell leukemia as recited in the preamble of the rejected claims (see applicant's remarks filed July 22, 2008, pages 14-16), applicant is directed to the teachings of Sykes put forth above and original claim 28 of Sykes. As is made clear from Sykes, the purpose of her invention is to allow transplanted allogeneic hematopoietic stem cells to mount a therapeutic graft-versus-host response while simultaneously inhibiting rejection of the transplanted allogeneic hematopoietic stem cells and reducing the incidence of frank GvHD.

Put another way, the combined references teach a method of treating adult T cell leukemia comprising administering hematopoietic stem cells and MEDI-507, and applicant has not put forth a convincing argument based on objective evidence and sound scientific reasoning to show that the limitations of the instant claims result in a manipulative difference in the method steps when compared to the teachings of the prior art. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Furthermore, the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See MPEP § 2144.

Insofar as applicant continues to argue that the claimed invention is distinguished over the prior art because it is "directed to a method…in which the antibody itself treats ATL," (see page 15, 3rd paragraph of applicant's remarks) this is not found convincing because the fact that applicant has recognized an advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See MPEP § 2145.

To conclude, the instant claims are rejected as unpatentable over Sykes in view of Borg, Bazin, and further in view of Taber's Cyclopedic Medical Dictionary, the definitions of "immunotherapy" found on the web according to Google.com as of November 9, 2008, Shirono, Branco and the instant specification.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 83-97, 106, 107, and 109-114 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating adult T-cell leukemia comprising administering an effective amount of a T-cell depleting anti-CD2 antibody comprising an Fc domain, or a T-cell depleting anti-CD2 antibody comprising the portion of the Fc domain which binds to FcR, or a T-cell depleting antigen binding fragment of an anti-CD2 antibody that does not comprise an Fc domain but is conjugated to a cytotoxic or radioactive moiety as recited in claims 102-105, ***does not reasonably provide enablement for*** a method of treating adult T-cell leukemia comprising administering an effective amount of an antigen binding fragment of an anti-CD2 antibody lacking the ability to bind FcRn, such as an Fab fragment or an scFv fragment not conjugated to a cytotoxic or radioactive moiety. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification exemplifies the treatment of a murine model of adult T-cell leukemia with MEDI-507/siplizumab and with an anti-IL-2Rα antibody known as "humanized anti-Tac", a.k.a., "HAT", a.k.a., "daclizumab" (see instant specification pages 119-122, Examples 6.1 - 6.22).

The instant claims, given their broadest reasonable interpretation consistent with the instant specification encompass in their breadth a method treating adult T-cell leukemia comprising administering an effective amount of any antigen binding fragment of an anti-CD2 antibody, such as an Fab fragment or an scFv fragment not conjugated to a therapeutic moiety (see instant specification, e.g., page 14, 2nd paragraph, page 44, last paragraph and claim 84).

However, according Branco et al. (Transplantation. 1999 Nov 27;68(10):1588-96), binding to FcRn is required for MEDI-507 to antagonize a mixed-lymphocyte reaction and for MEDI-507 to eliminate T cells (see column bridging paragraph on page 1594 to 2nd paragraph, right column). Moreover, given the inability of MEDI-507 to have any effect on cancer in a FcRγ knock out murine model of ATL as disclosed on page 123, 2nd paragraph of the instant specification, the skilled artisan would consider the treatment of ATL with anti-CD2 antibody fragments lacking FcRn binding ability to be fraught with uncertainty.

Given these considerations, the skilled artisan would not be able to practice the claimed method with an antigen binding fragment of an anti-CD2 antibody lacking the ability to bind FcRn, such as an Fab fragment or an scFv fragment, not conjugated to a therapeutic moiety in the absence of undue experimentation.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working

examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Examiner, Art Unit 1644
November 10, 2008